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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,790	03/11/2004	Satish Mahadeorao Totey	REL494/4-002US/58000	5605

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
09/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/798,790	TOTEY ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8,11-36 and 38* is/are rejected.

7)☒ Claim(s) *9,10,37 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/23/2004,12/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of claims 5-39 in the reply filed on 06/14/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The amendments of 06/29/2007 have been entered in full. Claims 1-4 and 40-44 are cancelled. Claims 5-39 are under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 recites the limitation "NCAM-positive cells" in claim 34. There is insufficient antecedent basis for this limitation in the claim. It appears that Applicants' intent was that claim 36 should depend from claim 35.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 5, wherein the differentiated neural cell population comprises at least about 60% dopaminergic neurons and/or at least about 30% serotonergic neurons, does not reasonably provide enablement for the method of claim 5, wherein the differentiated neural cell population comprises at least about 25% oligodendrocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

7. Claims 9, 10, and 11 are drawn to the method of claim 5, wherein the differentiated neural cell population comprises at least about 60% dopaminergic neurons, 30% serotonergic neurons, and 25% oligodendrocytes, respectively. A single method cannot yield a differentiated cell population that simultaneously meets the limitations of claim 9, 10, and 11, because the total comes to more than 100%. Claim 5 recites a method in which neuroprogenitor cells that are positive for nestin are selected, then enriched for NCAM-positive cells, and then cultured in a differentiation media which comprises TGF-β3 or interleukin-1β or both. Figure 10 of the instant specification depicts results of the procedure recited in claim 5; approximately 60% of the NCAM-positive cells were also immunopositive for TH; approximately 30% were immunopositive for Serotonin; and approximately 15% were immunopositive for GABA and glutamate; no oligodendrocytes are reported ([0050] in the published application). Thus, Fig. 10 is congruent with claim 5 and supports claims 9 and 10. A differentiated cell population comprising approximately 40% cells immunopositive for TH; approximately 30% immunopositive for Serotonin; and approximately 28% immunopositive for oligodendrocyte is shown in Fig. 11. Fig. 11 is not congruent with claim 5, because NCAM positive cells were not

selected. Therefore, the specification does not support the full scope of claims 9-11 because the specification teaches that the method of claim 5 does not work to yield a differentiated cell population that comprises at least about 25% oligodendrocytes.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated Rolletschek *et al.*, Mechanisms of Development (2001) 105:93-104 (of record). Claim 33 is drawn to a method of generating dopaminergic neurons from neuroprogenitor cells, comprising enriching the neuroprogenitor cells for cells that are positive for nestin, and differentiating the nestin-positive cells to generate dopaminergic neurons by culturing the cells in the presence of TGF-.beta.3 or interleukin-1.beta, or both. Claim 34 is drawn to the method of claim 33, wherein at least about 40% of the nestin-positive cells differentiate into dopaminergic neurons. Rolletschek *et al.* derived nestin+ neuroprogenitor cells from embryonic stem cells (paragraph bridging the columns on page 94) and teach that TGF-β3 and interleukin-1β promote differentiation of the selected cells to dopaminergic neurons (section 2.3, pages 94-96, and figures 4-7). Cell population with >40% dopaminergic neurons were obtained (p. 95 and Fig.4D).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5-8, 12-32, 35, 36,and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rolletschek *et al.*, Mechanisms of Development (2001) 105:93-104, as applied to claims 33 and 34 above, and further in view of WO 200188104, published November 22, 2001 (Carpenter; of record) and US 20020068045, (Reubinoff) published June 6, 2002.

12. As noted, Rolletschek *et al.* derived nestin+ neuroprogenitor cells from embryonic stem cells and teach that TGF-β3 and interleukin-1β promote differentiation of the cells to yield a population with >40% dopaminergic neurons, thereby anticipating the general methods of claim 33 and 34. Rolletschek *et al.* further teach that same protocol also yields serotonergic neurons (see Fig. 5D) as recited in instant claim 38. Culturing pluripotent embryonic stem cells to form embryoid bodies followed by culture in serum-free ITSFn medium to select nestin+ neural stem cells (instant claims 12-22), as well as expansion and differentiation of the selected neural progenitor cells in the presence of insulin, selenite, trransferrin, putrescine, GDNF, dbcAMP (instant claims 26-28 and 31) are well known in the art, as evidenced by Roletschek *et al.* in section 4.1, page 101. Rollotschek *et al.* passaged and cultivated selected cells for greater than 30 days (as in instant claim 27, 28, and 32; see Roletschek *et al.* Figs. 2-6).

13. The differences between the methods taught by Rollotschek *et al.* and the instant claims are: (1) Rolletschek *et al.* used, mouse, not primate or human embryonic stem cells as required in instant claims 5-32, and (2) Rolletschek *et al.* did not teach the additional enrichment for NCAM-positive cells recited in instant claims 5-32 and 35-39 (claim 36 is interpreted as depending from claim 35). Carpenter teaches selection of neural stem cells from human embryonic stem cells via embryoid body (EB) formation followed by cultivation and differentiation in a serum-free medium supplemented with fibronectin, bFGF and neurotrophic factors (as in instant claims 12, 13, 18, 26, 31) and magnetic bead sorting of NCAM+ cells (see Example 1, Table 3; Table 8; Figs. 1 and 3). The selected cells expressed nestin (Table 8, p. 26), and were capable of differentiation into neurons and glial cells, as expected for neural stem cells. Likewise, Reubinoff teaches that human embryonic stem cells cultured in serum-free medium (which permits embryoid bodies to form) differentiate into neural cells that are positive for both nestin and NCAM (see Fig. 5 and [0067]); the cells further differentiate into neurons (including TH+ neurons) and glia (Figs. 28 and 29). Reubinoff further teaches the common practices of cryopreserving cells (as in instant claim 29) and [0290] and laser dissection of blastocysts at (as in instant claims 6 and 8) at [0136].

14. Carpenter and Reubinoff teach the derivation of neural stem cells from human embryonic stem cells, and teach that such cells are positive for both nestin and NCAM. As either nestin or NCAM can be used to identify neural stem cells, it is obvious to use them both to provide further enrichment from a mixed population. While mouse and human pluripotent embryonic stem cells are notoriously different in their growth and differentiation requirements, the target for TGF-β3 and interleukin-1β taught in Rolletschek is not a pluripotent embryonic stem cell, but a multipotent, nestin positive neural stem cell. Therefore, one of skill in the art would have a

reasonable expectation of success in achieving differentiation of dopaminergic and serotonergic neurons by cultivating nestin and NCAM positive human cells, as taught by Carpenter and Reubinoff, in the presence of TGF-β3 and interleukin-1β, as taught in Rolletschek, to arrive at the generic methods of the instant claims. The specific high yields recited in instant claims 9, 10, 37, and 39 appear to be unprecedented and unexpected, therefore these claims are not rejected.

Conclusion

15. Claims 5-8, 11-36, and 38 are rejected.

16. Claim 9, 10, 37, and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DAVID ROMEO/
PRIMARY EXAMINER
ART UNIT 1647

DCG
Art Unit 1647
11 September 2007